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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,588	11/30/2001	Glenn J. Dorin	012441.00013	3451

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EXAMINER	
MITRA, RITA	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,588	DORIN ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/16/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-80,83-128 and 263-278* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-80, 83-128, 263-278* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/16/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction Election

Applicant's amendment in response to office action mailed August 11, 2004, filed on November 16, 2004 is acknowledged. Claims 1-70, 81, 82, 129-262 are canceled. Claims 71, 73, 74, 76, 77, 78, 79, 80, 86, 94, 95, 96, 97, 98, 108, 111, 118, 128 have been amended. New claims 263-278 have been added. Therefore, claims 71-80, 83-128 and 263-278 are currently pending and are under examination.

Response to Amendments and Remarks

Information Disclosure Statement:

The supplemental information disclosure statement filed on November 16, 2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609 because the copies of the references listed in PTO Form 1449 have not been submitted. Therefore the information referred to therein has not been considered as to the merits except in the US patent.

Objection to the Specification:

The objection is withdrawn in view of corrections in Table 1 and amendments to claims 71, 74, 77, 78, 108, 111 and 128.

Objection to the claims:

The objection is withdrawn in view of amendments to claims 76, 79, 80, 86, 94-98.

Claim Rejections - 35 USC § 112, Second Paragraph:

Rejection of claims 71-128 under 35 USC § 112, Second Paragraph is withdrawn in view of amendment to claims 71, 74, 77, 78, 108, 111, 115, 118 and 128.

Claim Rejections – 35 USC § 102:

Rejection of claims 78-80 and 110 under 35 USC § 102 is withdrawn in view of amendment to claim 78.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275 and 276 stand/are rejected under 35 USC 102(b) as being anticipated by WO 93/25230 (Broze et al., December 23, 1993). WO'230 teaches LACI at a concentration of 3.5 mg/ml in combination with 150 mM NaCl and 20 mM sodium sulfate. WO'230 also teaches the use of isotonic NaCl as a carrier (see page 20, lines 25-26 and page 29, line 32). LACI is a synonym for TFPI. Inherently because LACI and NaCl are present in the same concentrations claimed by the applicants, the NaCl of WO'230 acts as a solubilizing agent/ stabilizer for LACI to the same extent claimed by the applicants.

Applicants arguments have been considered but not found persuasive. Broze does not disclose specifically that the solution comprises arginine, however it is known in the literature that several amino acids serve as stabilizer or solubilizer (see Woog et al., col 9, lines 3-13). It should be noted that the rejection is on the basis of inherency. Broze teaches LACI at a concentration of 3.5 mg/ml in combination with 150 mM NaCl and 20 mM sodium sulfate. Thus Broze reference discloses all the elements of the claim except the element "from 200 mM

arginine to 300 mM arginine," which is inherent in the disclosure. Thus, Broze reference is anticipatory.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 73, 85 and 118 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/25230. Application of WO'230 is the same as in the above rejection of claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275 and 276 . WO'230 does not teach an LACI concentration of more than 3.5 mg/ml, does not teach NaCl concentrations of 0.5 M or greater, and does not teach pH's below 7.0 or 5.5. It would have been obvious to one of ordinary skill in the art at the time applicants' invention was made to form the LACI compositions of WO'230 having the concentrations and pH's outlined above because WO'230 is not limited to any particular concentrations or pH's (see page 29 line 1 to page 30 line 16) and discloses the need to optimize the concentrations depending upon the patient and mode of administration and because the concentration and pH are art-recognized result-effective variables which are routinely determined and optimized in the pharmaceutical art.

Claims 71, 73, 78, 83, 86, 87, 89 and 95-99, 111, 116, 119, 121 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/25230 as applied against claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275 and 276 above, and further in view of Woog et al.

WO'230 does not teach compositions including sucrose or glycine as stabilizers and solubilizers and including sodium phosphate as a buffer. Woog et al. teach that sucrose, polyethylene glycol and glycine are conventional stabilizers and solubilizers and that sodium phosphate and sodium citrate are conventional buffers for pharmaceutical compositions containing proteins (see column 7 lines 19-34, column 8 lines 48-54 and column 9 lines 1-14). Woog et al also teach arginine as the stabilizing or solubilizing agent (see column 9, lines 3-5). It would have been obvious to one of ordinary skill in the art at the time the applicants' invention was made to use in the LACI compositions of WO'230 the stabilizers, solubilizers, and buffers of Woog et al. because WO'230 discloses that the LACI can be formulated according to the known art (see page 29 lines 24-37), because Woog et al. disclose stabilizers, solubilizers and buffers which are generally applicable to pharmaceutical compositions containing proteins, and because it would be desirable to stabilize, solubilize and buffer LACI so that it will maintain it's pharmaceutical activity. It would further have been obvious to one of ordinary skill in the art at the time the applicants' invention was made to determine all operable and optimal concentrations of the components in the compositions outlined above because the concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical composition art.

Claims 71, 92, 102, 111, 112, 277 and 278 stand/are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 93/25230 as applied to claims 71, 73, 111, 114, 115, 118, 127, 128, 270, 271, 273, 275 and 276 above, and further in view of Patel. WO'230 does not teach histidine as a solubilizing agent. Patel teaches that histidine and methionine or a mixture thereof, which act as a stabilizer for aqueous solutions of proteins including interferon, GM-CSF or interleukin (see columns 2 and 4, Examples 1-4). Patel's solutions are stored for two weeks at 40 ^{0} C. It

would have been obvious to one of ordinary skill in the art at the time the applicants' invention was made to use in the LACI compositions of WO'230 the histidine of Patel as a stabilizer/ solubilizer, because Patel's histidine is generically applicable to all proteins (see column 1 lines 4-9), because a stabilizer which is operable for interferons, GM-CSF and interleukins would have been expected to be operable for all proteins because there is no structure in common among all interferons, GM-CSF and interleukins, because Patel's proposed stabilization mechanism (see column 3, lines 41-45) would be applicable to all proteins, and because it would be desirable to stabilize LACI and increase its stability level so that it will maintain it's pharmaceutical activity.

Claims 72-77, 79-110, 113, 117, 120, 122-126, 272, 274 are rejected as being dependent upon a rejected base claim.

Claim Rejections - Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 71, 73, 78, 79, 109, 110 and 263-269 stand/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 9, 33-37, and 41 of U.S. Patent No. 6,323,326. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 71, 73, 78, 79, 109, 110 and 263-

269 are directed to the broadest scope of the solution comprising a polypeptide selected from the group consisting of (i) human TFPI, (ii) ala-human TFPI and (iii) muteins of (i) or (ii). Claims 71, 73, 78, 79, 109, 110 and 263-269 encompass the TFPI amino acid sequences set forth in claims 1-5 and 9; and encompass the ala-TFPI amino acid sequence set forth in claims 33-37 and 41 of patent '326.

Claim 71 discloses a solution comprising from 200mM to 300 mM arginine, a polypeptide selected from the group consisting of (i) human TFPI, (ii) ala-human TFPI and (iii) muteins of (i) or (ii). This is an obvious variation of claims 1, and 33 in the patent '326, which discloses an aqueous formulation comprising TFPI and a charged polymer (claim 1 of '326) and wherein TFPI is Ala-TFPI (claim 33).

Claim 73 discloses a solution of claim 71 comprising from more than 0.2-20 mg/ml of said TFPI. This is an obvious variation of claims 1, 2, 3, 4 and 33, 34, 35 and 36 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 1 mg/ml (claim 1 of '326), greater than 5 mg/ml (claim 2 of '326) greater than 10 mg/ml (claim 3 of '326) greater than 20 mg/ml (claim 4 of '326) wherein TFPI of claims 1-4 is Ala-TFPI (claims 33-36).

Claim 78 discloses a solution comprising more than 0.2 mg/ml of TFPI selected from the group consisting of (i) human TFPI, (ii) ala-human TFPI and (iii) muteins of (i) or (ii) and further comprising a solubilizer selected from the group consisting of sucrose....polyphosphate....and sodium dodecyle sulfate. This is an obvious variation of claims 9 and 41 in the patent '326, which discloses an aqueous formulation comprising TFPI and a charged polymer, wherein charged polymer is polyphosphate (claim 9 of '326) and wherein TFPI is Ala-TFPI (claim 41).

Claim 79 discloses a solution of claim 78 wherein the polypeptide is present in a concentration from 1-20 mg/ml. This is an obvious variation of claim 3 and 35 in the patent '326, which discloses an aqueous formulation of claim 1 ('326), wherein the

concentration of TFPI is greater than 10 mg/ml (claim 3 of '326) and wherein TFPI is Ala-TFPI (claim 35).

Claim 109 discloses a solution of claim 108, which is pharmaceutically acceptable. This is an obvious variation of claim 5 and 37 in the patent '326, which discloses an aqueous formulation of claim 1 ('326), which is pharmaceutically acceptable (claim 5 of '326), and wherein TFPI is Ala-TFPI (claim 37).

Claim 110 discloses a solution of claims 78-107, which is pharmaceutically acceptable. This is an obvious variation of claim 5 and 37 in the patent '326, which discloses an aqueous formulation of claim 1 ('326), which is pharmaceutically acceptable (claim 5 of '326), and wherein TFPI is Ala-TFPI (claim 37).

Claim 263 discloses a solution of claim 71 comprising more than 1 mg/ml of said TFPI. This is an obvious variation of claims 1 and 33 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 1 mg/ml (claim 1 of '326), wherein TFPI of claim 1 is Ala-TFPI (claim 33).

Claim 264 discloses a solution of claim 263 comprising more than 5 mg/ml of said TFPI. This is an obvious variation of claims 2 and 34 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 5 mg/ml (claim 2 of '326), wherein TFPI of claim 2 is Ala-TFPI (claim 34).

Claim 265 discloses a solution of claim 264 comprising more than 10 mg/ml of said TFPI. This is an obvious variation of claims 3 and 35 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 10 mg/ml (claim 3 of '326), wherein TFPI of claim 3 is Ala-TFPI (claim 35).

Claim 266 discloses a solution of claim 265 comprising more than 20 mg/ml of said TFPI. This is an obvious variation of claims 4 and 36 in the patent '326, which discloses

an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 20 mg/ml (claim 4 of '326), wherein TFPI of claim 4 is Ala-TFPI (claim 36).

Claim 267 discloses a solution of claim 73 comprising from more than 0.2-20 mg/ml of said TFPI. This is an obvious variation of claims 1, 2, 3, 4 and 33, 34, 35 and 36 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 1 mg/ml (claim 1 of '326), greater than 5 mg/ml (claim 2 of '326) greater than 10 mg/ml (claim 3 of '326) greater than 20 mg/ml (claim 4 of '326) wherein TFPI of claims 1-4 is Ala-TFPI (claims 33-36).

Claim 268 discloses a solution of claim 267comprising from 1-10 mg/ml of said TFPI. This is an obvious variation of claims 1, 2, and 33, 34 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 1 mg/ml (claim 1 of '326), greater than 5 mg/ml (claim 2 of '326) wherein TFPI of claims 1-2 is Ala-TFPI (claims 33, 34).

Claim 269 discloses a solution of claim 267comprising from 5-20 mg/ml of said TFPI. This is an obvious variation of claims 3, and 35 in the patent '326, which discloses an aqueous formulation comprising TFPI wherein the concentration of TFPI is greater than 10 mg/ml (claim 3 of '326), wherein TFPI of claim 3 is Ala-TFPI (claim 35).

Thus, claims 71, 73, 78, 79, 109, 110 and 263-269 in present application and claims 1-5, 9, 33-37 and 41 in the patent '326 are obvious variations of a solution comprising, a polypeptide selected from the group consisting of (i) human TFPI, (ii) ala-human TFPI and (iii) muteins of (i) or (ii), wherein the solution comprises a solubilizer/stabilizer.

Conclusion

No claims are allowable.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (571) 272-0954. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Jon Weber, can be reached at (571) 272-0925. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0547.

Rita Mitra, Ph.D.
February 14, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER